7. (once amended) The method of claim 21, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

21. (once amended) A method for the reduction of lung inflammation caused by increased eosinophilia or of airway hyperreactivity, wherein said method comprises the administration of an active agent selected from the group consisting of mammalian calcitonin gene-related peptide (CGRP), adrenomedullin and mammalian diacetoamidomethyl cysteine calcitonin gene-related peptide ([Cys(ACM)^{2,7}]CGRP).

REMARKS

Claims 2, 4 to 8 and 21 are pending. Applicant has cancelled claims 3, 9 to 20 and 22 to 26 without prejudice or disclaimer, and amended claims 4, 6, 7 and 21. An Appendix including a marked-up copy of the amendments is attached, showing the changes. Former claims 2-26 are rejected under 35 USC §§ 112, 102 and 103. For the reasons outlined below, these rejections are respectfully traversed and reconsideration and withdrawal are respectfully requested.

Rejections Under 35 USC § 112

The Examiner has rejected claims 2-26, arguing that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the invention. The Examiner has referred to page 17 of the specification (lines 3-10) thus concluding that "CGRP" encompasses any peptide from any organism which shares significant structural and functional homology with the calcitonin gene-related peptide. According to the Examiner, the applicant has only disclosed a mammalian CGRP, adrenomedullin and mammalian [Cys(ACM)^{2,7}]CGRP. In response, claim 21 has been amended to recite mammalian CGRP, adrenomedullin and

mammalian [Cys(ACM)^{2,7}]CGRP, and claim 4 has been amended to recite mammalian CGRP. Further, claims 4, 6 and 7 have been amended to depend from claim 21, and claims 3, 9 to 20, and 22 to 26 have been removed. Applicant reserves the right to pursue any subject matter removed by these amendments in one or more continuation applications. In light of the above, applicant respectfully requests that the rejection be withdrawn.

The Examiner has further rejected claims 2-26 pursuant to 35 USC § 112 based on the use of the term "prevention", arguing that the specification does not reasonably provide enablement for the method of prevention of the pathophysiological manifestations of the recited diseases. In response, applicant first wishes to note that claim 21 and dependent claims 2 to 20 do not recite the term "prevention" and therefore respectfully submits that the rejection is inapplicable with respect to these claims. Regarding claims 22 to 26, the applicant notes that claims 22 to 26 have been deleted as noted above. Therefore, in light of the above, the applicant respectfully requests that the rejection be withdrawn.

In addition, the Examiner further refers to the definition of "CGRP" on page 17 in this regard. In response, page 17 has been amended to limit the definition of CGRP to calcitonin gene-related peptide *per se*.

Rejections Under 35 USC § 102

The Examiner has rejected claims 2-26 as anticipated in light of United States Patent No. 5,858,978 as evidenced by *The Merck Manual*. In response, the applicant respectfully submits the following.

Applicant first wishes to reiterate his contention that the '978 Patent is not enabling with regard to the use of CGRP for the reduction of lung inflammation caused by increased eosinophilia or of airway hyperreactivity and thus does not teach the use of CGRP for this purpose. As discussed in applicant's letter of December 4, 2000, the '978

Patent only describes a relationship (observed *in vitro*) between CGRP and an inhibition of IL-1, via a cAMP-mediated mechanism. The '978 Patent then further mentions in general terms a relationship between cytokine release and inflammatory reactions and in turn recites a number of diseases which may involve inflammation, with asthma being one example of many such diseases. As noted in applicant's letter of December 4, 2000, numerous differences exist between the subject matter disclosed in the '978 Patent and the findings described in the instant application.

Applicant further wishes to note that the Examiner has referred to *The Merck Manual* to expand the definition of asthma beyond that recited in the '978 Patent. This combination of references is not believed to be appropriate under 35 USC § 102.

Furthermore, by such reference, it is assumed that the Examiner considers the information presented in *The Merck Manual* to reflect the general common knowledge of the art. In this regard, applicant notes that *The Merck Manual* also indicates, as is indeed generally known in the art, that CGRP is known to cause bronchoconstriction (see page 557, right column, last paragraph), which was in fact the state of the knowledge in the art prior to the instant applicant's findings. The instant applicant, alternatively, was the first to directly test the effects of CGRP on animal airways and thus discovered that its effects were precisely opposite to the conventional wisdom in the art. Therefore, while the Examiner apparently relies on *The Merck Manual* to expand the definition of asthma possibly to encompass some of the terms recited in earlier versions of the claims, the applicant respectfully submits that the Examiner fails equally to consider that *The Merck Manual* directly teaches against a use of CGRP for the treatment of asthma as allegedly disclosed in the '978 Patent.

Applicant respectfully submits that he was the first to recognize, demonstrate (including *in vivo* results), and describe the claimed activity for CGRP (namely in the reduction of lung inflammation caused by increased eosinophilia or of airway hyperreactivity). Applicant has demonstrated that CGRP protects against a wide variety of bronchoconstrictor stimuli (e.g. substance P, metacholine, allergen challenge, etc.),

and reduces eosinophil accumulation in the bronchial walls and bronchospastic airway responses such as reversible airway hyperreactivity. Therefore, claim 21 has been amended to recite a method for the reduction of airway hyperreactivity and for the reduction of lung inflammation caused by increased eosinophelia. This amendment is supported by, for example, pages 2 (lines 9-14), 8 (line 25) to 9 (line 1), 15 (lines 27-29), 16 (lines 6-7), 31 (lines 8-11) and 31 (lines 2-7). Further, applicant is the first to describe CGRP activation of the chemotaxis of eosinophils from the bronchial mucosa (see Example 3 [page 33, lines 13 to 15 in particular]).

Applicant respectfully submits that claim 21 as amended is novel over the '978 patent. Further, claims 4, 6 and 7 have been amended to depend from claim 21 and thus incorporate the changes therein, and claims 3, 9 to 20, and 22 to 26 have been removed as noted above. In light of the above, applicant respectfully requests that the objection be withdrawn.

Rejections Under 35 USC § 103

The Examiner has rejected claims 2-26 as obvious in light of the '978 Patent discussed above in view of United States Patent No. 5, 510, 339. In response, the Applicant respectfully submits the following.

As set forth in applicant's letter of December 4, 2000, the applicant first wishes to reiterate that, in his view, the Examiner has not fulfilled the criteria to establish a *prima facie* case of obviousness.

Based on the above comments relating to the novelty rejection in light of the '978 patent, applicant respectfully submits that the features recited in the claims as amended are not disclosed in the '978 Patent. Therefore, applicant respectfully submits that a combination of these references in this regard is no longer applicable, and respectfully requests that the rejection be withdrawn.

It is believed this responds to all of the Examiner's concerns, however if the Examiner has any further questions, he is invited to contact Joy Morrow at 613-232-2486. Further, If the Examiner does not consider that the application is in a form for allowance, an interview with the Examiner is respectfully requested.

Respectfully submitted,

August 14, 2001
Date

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Appendix

present invention is most useful in the prevention and management of both acute and chronic conditions.

The term "CGRP" as used herein means a calcitonin gene-related peptide, which is a neuropeptide produced by stimulated mammalian sensory nerve fibers and neuroendocrine cells. ~~This term is also intended to~~ CGRP homologs or CGRP-like peptides include any peptide which shares significant structural and functional homology with the calcitonin gene-related peptide set forth in the present invention i.e., functions as CGRP. CGRP homolog means any other natural peptide produced within a mammalian organism that is structurally related to CGRP (i.e., that shares similar amino acid sequences and that is classified into the same family of peptides). For example, the amino acid sequences of CGRP peptides are very well conserved (85-98% homology) among mammalian species and all CGRPs are members of the calcitonin family of peptides. This calcitonin family of peptides also includes the related peptide amylin (46% homology with CGRPs), salmon calcitonin (32% homology with CGRPs) and adrenomedullin (24% homology with CGRPs). All these peptides belonging to the calcitonin family of peptides have in general a N-terminal ring structure of 6-7 amino acids involving a disulfide bridge and an amidated C-terminal end. Because of these common structural features, all of them can cross-react to a varying extent with each other's receptors and induce the same effects. Examples of cross reaction between these peptides include, among others, regulation of cardiovascular homeostasis (CGRP, amylin, calcitonin, adrenomedullin), modulation of glycogen metabolism (amylin, calcitonin, CGRP) and production of hypocalcemic effects (calcitonin, CGRP, amylin). The essential functional aspect of these CGRP-like peptides in the context of the present invention is that when administered to a mammal, they might be capable of binding the receptors that are activated by CGRP and consequently to initiate similar bronchoprotector and anti-inflammatory effects.

What is claimed is:

1. A method for the prophylaxis or treatment of asthma, bronchospastic diseases characterized by airway hyperreactivity or lung inflammatory reaction characterized by increased eosinophilia comprising the administration of an active agent selected from the group consisting of CGRP, CGRP natural homologs, CGRP analogs, the analogs of CGRP's natural homologs, CGRP fragments, the fragments of CGRP's natural homologs, CGRP natural derivatives and the natural derivatives of CGRP's natural homologs.

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2. The method of claim 21, wherein said administration is via a pulmonary route.

amended 04 Dec 00

3. The method of claim 21, wherein said administration of said active agent is for the prophylaxis or treatment of asthma.

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4. The method of claim 21, wherein said active agent is mammalian CGRP.

amended 14 Aug 01

5. The method of claim 4, wherein said administration is via a pulmonary route.

6. The method of claim 21, wherein said active agent has a purity of at least about 95 to 98 %.

amended 14 Aug 01

7. The method of claim 21, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

amended 14 Aug 01

8. The method of claim 7, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or

dry powder comprising said active agent for inhalation by said mammal.

9. The method of claim 21, wherein said administration of said active agent is for the prophylaxis or treatment of bronchospastic diseases characterized by airway hyperreactivity.

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10. The method of claim 9, wherein said active agent is CGRP.

11. The method of claim 10, wherein said administration is via a pulmonary route.

12. The method of claim 9, wherein said active agent has a purity of at least about 95 to 98 %.

13. The method of claim 9, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

14. The method of claim 13, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or dry powder comprising said active agent for inhalation by said mammal.

15. The method of claim 21, wherein said administration of said active agent is for the prophylaxis or treatment of lung inflammatory reaction characterized by increased eosinophilia.

16. The method of claim 15, wherein said active agent is CGRP.

17. The method of claim 16, wherein said administration is via a pulmonary route.

18. The method of claim 15, wherein said active agent has a purity of at least about 95 to 98 %.

19. The method of claim 15, wherein said active agent is dispersed within a composition comprising a pharmaceutically acceptable excipient, liquid or solid carrier.

20. The method of claim 19, wherein said composition is in a form suitable to be introduced into a mammal by providing an aerosol or dry powder comprising said active agent for inhalation by said mammal.

21. A method for the ~~treatment of a disease selected from asthma, bronchospastic diseases characterized by airway hyperreactivity, and lung inflammatory diseases characterized by increased eosinophilia~~ reduction of lung inflammation caused by increased eosinophilia or of airway hyperreactivity, wherein said method comprises the administration of an active agent selected from the group consisting of ~~CGRP~~ mammalian calcitonin gene-related peptide (CGRP), adrenomedullin and [Cys(ACM)^{2,7}]CGRP ~~)~~.

22. A method for the prevention or treatment of the pathophysiological manifestations of a disease selected from asthma, bronchospastic diseases characterized by airway hyperreactivity, and lung inflammatory diseases characterized by increased eosinophilia, wherein said method comprises the administration of an active agent selected from the group consisting of CGRP, adrenomedullin and [Cys(ACM)^{2,7}]CGRP, mammalian diacetoamidomethyl cysteine calcitonin gene-related peptide(

23. The method of claim 22, wherein said administration is via a pulmonary route.

24. The method of claim 22, wherein said administration of said active agent is for the prevention or treatment of the pathophysiological manifestations of asthma.

25. The method of claim 22, wherein said active agent is CGRP.

26. The method of claim 22, wherein said pathophysiological manifestations are selected from the group consisting of:

(a) reversible airway obstruction,

(b) airway hyperreactivity, and

(c) lung inflammatory reaction characterized by increased eosinophilia.—